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California Stress, Trauma, and Resilience Study (CalSTARS) protocol: A multiomics-based cross-sectional investigation and randomized controlled trial to elucidate the biology of ACEs and test a precision intervention for reducing stress and enhancing resilience

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ABSTRACT

Adverse Childhood Experiences (ACEs) are very common and presently implicated in 9 out of 10 leading causes of death in the United States. Despite this fact, our mechanistic understanding of how ACEs impact health is limited. Moreover, interventions for reducing stress presently use a one-size-fits-all approach that involves no treatment tailoring or precision. To address these issues, we developed a combined cross-sectional study and randomized controlled trial, called the California Stress, Trauma, and Resilience Study (CalSTARS), to (a) characterize how ACEs influence multisystem biological functioning in adults with all levels of ACE burden and current perceived stress, using multiomics and other complementary approaches, and (b) test the efficacy of our new California **Prec**ision **I**ntervention for **S**tress and R**e**silience (PRECISE) in adults with elevated perceived stress levels who have experienced the full range of ACEs. The primary trial outcome is perceived stress, and the secondary outcomes span a variety of psychological, emotional, biological, and behavioral variables, as assessed using self-report measures, wearable technologies, and extensive biospecimens (i.e. DNA, saliva, blood, urine, & stool) that will be subjected to genomic, transcriptomic, proteomic, metabolomic, lipidomic, immunomic, and metagenomic/microbiome analysis. In this protocol paper, we describe the scientific gaps motivating this study as well as the sample, study design, procedures, measures, and planned analyses. Ultimately, our goal is to leverage the power of cutting-edge tools from psychology, multiomics, precision medicine, and translational bioinformatics to identify social, molecular, and immunological processes that can be targeted to reduce stress-related disease risk and enhance biopsychosocial resilience in individuals and communities worldwide.

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Introduction

Over the past 35 years, research has consistently shown that adverse childhood experiences (ACEs) have a deleterious impact on almost all major mental, physical, and behavioral indicators of wellbeing across the lifespan (Herzog & Schmahl, 2018; Waehrer et al., 2020; Webster, 2022). ACEs include highly stressful, sometimes traumatic adversities such as childhood maltreatment (e.g. emotional and physical abuse, neglect) and household dysfunction (e.g. divorce, household violence)

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that occur before age 18. These stressors have been shown to alter psychological and emotional processes that increase individuals' risk of developing mental and physical health problems (Felitti et al., 1998; Giano et al., 2020; Hughes et al., 2017; Webster, 2022).

ACEs and major life stress exposure are also hypothesized to dysregulate key biological processes. When an individual experiences chronic or severe forms of adversity, particularly in early life, it can lead to altered brain and body dynamics that negatively impact lifelong health (Franke, 2014). This stress-related biological dysfunction, sometimes referred to as *toxic stress physiology*, describes the common biological outcomes associated with the excessive activation of stress response systems by recurrent or chronic stressors (Gilgoff et al., 2024; National Scientific Council of the Developing Child, 2005/2014). These outcomes include alterations in stress and immune processes that increase the risk for several chronic diseases and early mortality (Franke, 2014; Furman et al., 2019; Slavich, 2015; Slavich & Auerbach, 2018).

Despite general awareness that ACEs are a critical public health issue (Bhushan et al., 2020; McBain et al., 2023), the biopsychosocial processes linking ACEs with lifelong disease risk are poorly understood. This has occurred partly because instead of using a systems biology-based approach to studying ACEs and health, most research on ACEs to date has focused on a few select biological systems, typically studied independently, to elucidate potential mechanisms linking ACEs and disease risk. Moreover, studies that have examined the interaction of multiple biological systems simultaneously have generally been limited by small sample sizes. As a result of these limitations, there is a pressing need for larger, multisystem-based studies investigating how various biopsychosocial systems influence one another, and how such dynamics are shaped by early life as well as lifelong stressor exposure.

Beyond advancing the basic science of stress and resilience, such work provides a stepping stone toward developing effective precision medicine-based approaches to treating stress that move away from a "one-size-fits-all" approach and toward treatment selection that is based on carefully profiling which biobehavioral processes are most severely dysregulated for each patient. The rationale for adopting a treatment approach that profiles specific biobehavioral processes is grounded in the understanding that ACEs, by definition, occur in early life, making it impossible to directly intervene on ACEs themselves in adulthood. Reducing the impact of ACEs on physical and mental health in adulthood thus involves reducing adults' heightened perceptions of stress and normalizing dysregulated biobehavioral processes attributable to ACEs. As ACEs are known to strongly correlate with perceived stress levels in adulthood (Shonkoff et al., 2012), a primary focus on reducing adults' perceived stress is a logical treatment outcome for studies seeking to mitigate the long-term psychological and biological impacts of early-life ACE exposure.

To address these issues, we designed a highly integrative cross-sectional study paired with a randomized controlled trial (RCT) – collectively called the **Cal**ifornia **S**tress, **T**rauma, **a**nd **R**esilience **S**tudy (CalSTARS) – to identify social, molecular, and immunological processes for mitigating stress-related dysfunction and enhancing biopsychosocial resilience. The purpose of this article is to describe the study rationale and protocol to maximize scientific transparency and reproducibility. First, we summarize existing research linking ACEs with health-relevant biological changes and describe the main empirical gaps we see in this work. In doing so, we highlight the benefits of using multiomic approaches to studying multisystem processes linking ACEs and health, and the benefits of using both personalized and precision medicine-based approaches when intervening to improve stress-related dysfunction. Second, we describe the highly integrative, multi-method, multi-modal study protocol, which aims to (a) characterize how ACEs shape multisystem biological functioning in adults with all levels of ACE burden and current perceived stress, using multiomics and other complementary approaches, and (b) test the efficacy of our new California **Prec**ision **I**ntervention for **S**tress and R**e**silience (PRECISE) in adults with elevated perceived stress levels who have experienced the full range of ACEs. As we describe in greater detail below, the primary trial outcome is perceived stress and the secondary outcomes span a variety of psychological, emotional, biological, and behavioral variables, as assessed using self-report measures, wearable technologies, and extensive biospecimens (i.e. DNA, saliva, blood, urine, & stool) that will be subjected to genomic, transcriptomic, proteomic, metabolomic, lipidomic, immunomic, and metagenomic/microbiomic analysis. Our ultimate goal in conducting this work is to leverage the power of cutting-edge tools from psychology, multiomics, precision medicine, and translational bioinformatics to identify social, molecular, and immunological processes that can be targeted to reduce stress-related disease risk and enhance biopsychosocial resilience in individuals and communities worldwide.

ACEs and stress-related dysfunction are common and have far-reaching consequences

ACEs are alarmingly prevalent in the United States and are presently implicated in 9 out of 10 leading causes of death, including heart disease, stroke, cancer, chronic obstructive pulmonary disease (COPD), diabetes, Alzhiemier's, and suicide (California Department Public Health, Injury and Violence Prevention Branch, et al., 2020). Indeed, the Centers for Disease Control and Prevention (CDC) Behavioral Risk Factor Surveillance System revealed that 62% of adults in California have experienced at least one ACE and 16% have experienced four or more ACEs (California Department Public Health, Injury and Violence Prevention Branch, et al., 2020). In turn, research has shown that adults with a history of ACEs often present with complex clinical profiles marked by co-occurring psychiatric disorders (e.g. posttraumatic stress disorder, depression, borderline personality disorder) and chronic diseases (e.g. obesity, diabetes) (Herzog & Schmahl, 2018; Waehrer et al., 2020). A systematic review and meta-analysis revealed that individuals with four or more ACEs also have an increased risk of problematic drug and

alcohol use, violence, and sexual risk taking (Hughes et al., 2017). Additionally, ACEs have moderately strong associations with risk for cancer, heart disease, and respiratory disease (Hughes et al., 2017), as well as with disturbances in cognitive and affective processing such as heightened attention to threatening stimuli, increased loneliness, and impaired social cognitive functioning and interactions, including aggressive behaviors (Birn et al., 2017; Herzog & Schmahl, 2018). Importantly, these effects do not end in childhood but rather continue to persist over the entire lifespan (McGinnis et al., 2022; van der Velden et al., 2022).

Beyond their impacts on personal health and well-being, ACEs have profound societal and economic implications. The annual health costs associated with ACEs in North America and Europe is estimated to be a staggering $1.3 trillion USD (Bhushan et al., 2020). Notably, the State of California alone bears $112.5 billion USD per year of this cost, with projections indicating the annual health costs associated with ACEs in California will surge to $1.2 trillion USD over the next decade (Bhushan et al., 2020; Miller et al., 2020).

Moreover, ACEs have a profound socioeconomic impact on individuals. For example, those who have experienced a higher ACE burden have poorer health care access (Hargreaves et al., 2019; Schüssler-Fiorenza Rose et al., 2022), greater housing and food insecurity (Jackson et al., 2019), and lower educational and economic attainment (Currie & Widom, 2010; Sansone et al., 2012). In the U.S., the strongest drivers of disparities in life expectancy between counties are race/ethnicity, socioeconomic status, behavioral and metabolic factors, and health care quality and access. The combination of these factors accounts for a substantial 74% of the variability in life expectancy at birth (Dwyer-Lindgren et al., 2017). Notably, adults reporting three or more ACEs face a substantial 9.5-year decrease in quality-adjusted life expectancy, in contrast to a modest 1.7-year decrease among those reporting 1–2 ACEs (Jia & Lubetkin, 2020). ACEs thus represent one of the most burdensome, costly, and lethal social and medical challenges confronting us today.

Empirical gaps: Understanding multisystem mechanisms linking ACEs & health

Although the number of studies investigating the impact of ACEs on health, disease, and wellbeing has increased in recent years, there are still many gaps in our understanding of the mechanistic pathways linking ACEs with adult outcomes. ACEs have been associated with alterations in stress-responsive systems including the hypothalamic-pituitary-adrenal (HPA) axis (Kalmakis et al., 2015) and immune system, leading to elevated proinflammatory cytokine and C-reactive protein levels (Coelho et al., 2014). In addition, ACEs have been found to be related to structural and functional changes in the brain (Soares et al., 2021), including in key circuits involved in stress reactivity such as the prefrontal cortex (PFC), hippocampus, amygdala, and striatal circuits (Smith & Pollak, 2020). ACEs may also exert long-term—even multi-generational—effects on these systems through epigenetic mechanisms, such as DNA methylation (Neves et al., 2021).

Although informative, most studies investigating the biological effects of ACEs have focused on one potential system, such as the immune system or HPA axis, and have involved a select number of biomarkers, with C-reactive protein, interleukin-6, and tumor necrosis factor-α being the most widely reported inflammatory biomarkers (Coelho et al., 2014; Kerr et al., 2021), and cortisol being a commonly measured biomarker of HPA axis function (Deighton et al., 2018; Kerr et al., 2021). Even studies looking at genetic and epigenetic factors have frequently focused on candidate genes rather than taking a more comprehensive approach. In contrast to this work, recent advances in systems biology have illustrated the value of multiomics approaches for investigating complex biological dynamics and their impact on health (Maitre et al., 2022; Schüssler-Fiorenza Rose et al., 2019). Omics measures include genomics (study of genes), epigenomics (studies on markers on genes that affect gene expression), transcriptomics (studies of RNA), proteomics (studies of proteins), metabolomics (studies of small molecules), and the microbiome (studies of microorganisms that live in and on our body), and combining metrics across these different domains can yield a high-resolution picture of biological functioning, as well as how such functioning is both shaped by ACEs and predictive of health.

Recent research has begun illustrating the power of omics and multiomics approaches for characterizing how multiple biological systems collectively shape health and disease (Mengelkoch et al., 2023a, 2023b, 2024; Slavich et al., 2023). One study using gene expression data found that participants with PTSD who were matched for adult PTSD severity and trauma exposure, but who were exposed to different adverse childhood events, had markedly different gene expression profiles (Mehta et al., 2013). Another recent study used proteomics to examine differences in proteins related to mitochondrial biology, inflammatory biology, and cellular metabolism between participants exposed to ACEs and those who had not been exposed (Zang et al., 2023). In addition, research has revealed differences in the gut microbiome compositions of adults with different ACE exposure histories (Hantsoo et al., 2019), with adults with high ACE exposure having a higher proportion of Prevotella, which has been associated with chronic inflammation in other studies (Larsen, 2017). These alterations can affect how vagal, neuroendocrine, and immune system (i.e. gut-brain axis) processes interact, which could in turn have substantial implications for lifelong health.

ACEs are also an important focal point for understanding how stress occurring in adulthood affects health for several reasons. First, ACEs can shape how adults respond to stressors, since trauma during developmentally sensitive periods can affect stress responsiveness later in life (Bunea et al., 2017; Danese & Lewis, 2017; Stevens et al., 2018). Second, ACEs contribute to an individuals' total lifetime stressor burden and allostatic load, thus increasing the risk for stress-related biological dysfunction in adulthood (Shields & Slavich, 2017). Finally, ACEs can be a risk factor for adult trauma and life stressors insofar as adults who have experienced ACEs are more likely to experience trauma and chronic stress in adulthood (Ports et al., 2016).

Similar to ACEs, the literature on the biological effects of chronic adult stress, lifetime stress burden, and allostatic load has mainly focused on select biological markers related to inflammation, the HPA axis, and cardiovascular functioning. Indeed, there are only a few multiomics studies of chronic adult stress, and those have primarily used animal models (Li et al., 2021; Misiewicz et al., 2019). Hence, there is a pressing need to understand not only the biological and physiological signatures of ACEs and total lifetime stressor burden, but also how these dynamics shape levels of perceived stress in adulthood.

An additional gap in the literature on ACEs involves a dearth of research examining how ACEs interact with other types of social and environmental exposures to shape health and wellbeing in adulthood. Despite general knowledge that communities that have higher rates of ACEs also have higher rates of exposure to chemicals, air pollution, discrimination, and general unpredictability (Gladieux et al., 2023; Olvera Alvarez et al., 2018), almost no research has examined how the combination of these various risk factors, in conjunction with ACEs, predicts adulthood health. Therefore, a comprehensive approach to understanding the impact of ACEs must involve not only a systems biology approach powered by individual-focused multiomics techniques but also a contextual approach that assesses the surrounding environment in which the person lives and that integrates into the equation the exposome, including pollution and other environmental contaminant exposures (see Slavich, 2020, 2022; Slavich et al., 2023).

Precision and personalized approaches to stress management

In terms of treating individuals exposed to ACEs and other forms of early life adversity, it is well known that an individual's biological predisposition and life stressor exposure are important considerations that interact to influence risk for poor health (i.e. diathesis-stress model). For example, some individuals have genetic profiles that increase their susceptibility to developing certain disorders such as depression, schizophrenia, anxiety disorders, and eating disorders following exposure to stressful life events (Broerman, 2017). In the context of ACEs, an abundance of research has examined how biological factors, environmental exposures, and the interaction of the two can lead to increased risks for health problems (Berens et al., 2017; Gladieux et al., 2023; Soares et al., 2021). On this matter, we recognize that it is equally important to study frameworks that can build resilience to reduce stress and maintain well-being as we develop clearer mechanistic insights (Gilgoff et al., 2024). However, intervention approaches aimed at reducing stress and building resilience are understudied, especially in adult populations. And yet, research has shown that ACEs are inversely associated with resilience in adults, with increasing counts of ACEs linked to worse coping and adult resilience (Daniel et al., 2020; Daníelsdóttir et al., 2022).

As a result of these limitations, tailored interventions for reducing health risks and stress levels, and building resilience amongst adults who experience stress-related effects, is an area that requires more attention. In the broader context, it is important to recognize that each person has a unique clinical profile, necessitating comprehensive assessments to provide optimal treatments that alleviate perceived stress and other factors that drive stress-related disease pathophysiology. Consequently, a thorough profiling of individuals is essential to comprehend the many ways in which a person's history, biology, and environment interact to shape their physical and mental wellbeing, and what we can do to build greater psychosocial resilience.

Over the past decade, interest in using precision medicine approaches to treat costly diseases such as cancer has increased greatly. Precision medicine is an innovative approach that tailors disease prevention and treatment by considering variations in individuals' risk and resilience profiles, including their life stressors, genetics, environmental exposures, and lifestyles (Delpierre & Lefèvre, 2023). In the context of cancer, for example, precision oncology has shown great promise in revolutionizing cancer care by analyzing the genetic sequence of a patient's tumor, investigating its metabolic processes, and monitoring the immune system's response to the tumor and treatment (Hoeben et al., 2021).

Beyond the provision of tailored treatments, precision medicine has the potential to reduce the economic costs of ACEs. In a systematic review on the cost-effectiveness of precision medicine, the authors concluded that the vast majority of studies (59 in total) indicated that precision medicine interventions are generally more cost-effective compared to conventional care (Kasztura et al., 2019). It is essential to acknowledge, however, that several factors warrant consideration during precision medicine economic evaluations, as they can impact cost-effectiveness. These factors include but are not limited to, the expenses associated with companion treatments, the accuracy and cost of the test, and the timing of testing in relation to the patient's age (Kasztura et al., 2019).

Similarly, there has been increased interest in precision health, a broader concept encompassing self-directed approaches that individuals can take to safeguard their own well-being. An example of precision health is when a person uses mobile health applications on their smart device(s) to track their own physical activity, blood pressure, or nutrition in order to guide lifestyle choices (CDC, 2022). Although interest in personalized and tailored treatments has been growing in mental health care settings, there is still a general lack of research aimed at understanding how stress management interventions may be tailored to maximally mitigate health risks, normalize stress-related dysfunction, and promote healthy living based on each person's unique biopsychosocial profile.

Moreover, despite the sizable social and economic costs of ACEs, the biobehavioral processes linking ACEs and lifelong disease risk are poorly understood. As a result, no model exists for reducing stress-related disease risk based on an individual's personal profile. In current psychosocial treatment approaches for stress-related health problems, interventions are not selected by carefully profiling individuals but rather based on generalized protocols and population averages: a

one-size-fits-all approach. Although many stress management strategies exist including mindfulness, biofeedback, cognitive behavior therapy, and others, most of these approaches are not personalized to fit an individual's specific goals or needs. For instance, whereas one person may experience ACE-associated dysregulation in key cognitive processes (e.g. negative thinking, rumination), another may primarily experience health-damaging changes in social routine (e.g. socially isolating), diet (e.g. under- or over-eating, consuming pro-inflammatory foods), sleep (e.g. difficulty falling or staying asleep, early awakening), or physical activity (e.g. living a sedentary lifestyle). Consequently, existing interventions do not always successfully ameliorate stress levels, perhaps because they do not consider key individual differences.

Summary

To summarize, although ACEs and stress-related dysfunction lead to significant disparities in human health and wellbeing, we presently lack a full understanding of the biopsychosocial mechanisms underlying these effects. The field also lacks a precision medicine approach to addressing ACE-associated disparities. Additional well-powered, multiomics research is needed to address the former issue, and well-controlled clinical trials are needed to address the second issue and determine whether accurately profiling individuals–and matching people to their optimal intervention based on these profiles–improves treatment outcomes. To address these two points, we designed the CalSTARS to investigate (a) the multisystem mechanisms linking ACEs, perceived stress, and health, and (b) whether a precision stress management program that we developed successfully reduces perceived stress levels and fosters biopsychosocial resilience. In pairing multiomics with a precision stress management intervention, we aim to both produce novel insights into the biological pathways linking early adversity and adulthood health, and to examine if—and, if so, how—ameliorating stress using a highly novel precision treatment strategy normalizes biopsychosocial functioning and enhances resilience.

Study protocol: PRECISE overview and objectives

CalSTARS uses tools from precision medicine (i.e. elucidating mechanisms to help predict, prevent, and manage stress) and precision health (i.e. enabling individuals to take actions of their own using a stress-reduction intervention) to mitigate stress and improve health. The first part of CalSTARS is a cross-sectional assessment that involves profiling individuals based on their early-life and total lifetime stressor exposure, as well as their risk and resilience factors, to understand biopsychosocial processes that potentially link ACEs and health. To accomplish this goal, the study will also characterize multiomic profiles (i.e. genome, transcriptome, proteome, metabolome, lipidome, immunome, and metagenome/microbiome) and their relation to ACEs, lifetime stressor exposure, and chemical and other environmental exposures. Although there is a sizable literature linking ACEs to chronic health outcomes in adults and altered immune systems, almost no research has applied a multi-method, multiomics approach to investigating how ACEs impact adult health. To fully address this issue, therefore, the cross-sectional portion of CalSTARS will recruit adults with all levels of (past) ACE burden and current perceived stress.

The second part of CalSTARS is a longitudinal RCT that involves testing a novel precision stress management intervention program that we developed to reduce individuals' stress levels and increase their biopsychosocial resilience. As described in greater detail below, participants in the intervention arms will receive the intervention type that addresses their main biobehavioral problem area. These participants, as well as those in an active control and passive control group, will be recruited for having elevated perceived stress levels (i.e. the primary trial outcome) and the full range of ACEs, and they will be comprehensively assessed at baseline in addition to three months later (immediate post-intervention follow-up for those receiving treatment) and six months later (three-month, post-intervention delayed follow-up for those receiving treatment). This protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines for RCTs (Supplement 1; Butcher et al., 2022; Chan et al., 2013) and was pre-registered on ClinicalTrials.gov (NCT06063174).

Method

Participants

To accomplish these main objectives, we will recruit 725 adults residing in California. All 725 participants will complete baseline assessments (see below) to comprehensively assess their ACEs and lifetime stressor exposure. Among these adults, 425 will participate in a RCT to assess the efficacy of the PRECISE as compared to an active and passive control arm. The remaining 300 participants, who will only complete the baseline assessments, will be included to enhance statistical power for analyzing cross-sectional associations between ACEs and participants' psychological, multiomics, and clinical profiles. Randomization will be carried out in a 3:1:1 ratio for the intervention arm, passive control arm, and active control arm, respectively.

Eligibility and exclusion criteria

To be eligible for CalSTARS, potential participants must be at least 18 years old, proficient in English, reside in California, and willing to provide blood sample(s) and wear a smartwatch for the duration of the study. All genders, ethnicities, and races will be eligible, and participants will perform all study activities remotely. Exclusion criteria include a history of human immunodeficiency virus (HIV) types 1 or 2 antibodies, a heart attack or stroke within the past year, cancer diagnosis or treatment within the past two years, or medications known to influence inflammation in the past month (see Table 1). To be eligible for the RCT, participants will also need to have a score greater than 15 on the Perceived Stress Scale (PSS-10) and a score greater than five in at least one domain on the

Table 1. Study inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
General study criteria • Proficient in English • At least 18 years old • Reside in California • Willing to provide blood sample(s) and wear a smartwatch	**Medical/Disease history** • Has a positive test result for human immunodeficiency virus (HIV) types 1 or 2 antibodies • Has had a heart attack or stroke within the past year • Has had and/or been treated for any type of cancer in the past two years

Additional RCT study criteria
• Screening score >15 on Perceived Stress Scale (PSS-10)
• Screening score >5 in at least one Consequences of Stress Scale (CSS) domain
	Medication usage
	Has taken any of the following medications over the past month:
	• Prednisolone (e.g. Omnipred, Pred Mild, Pred Forte, Orapred ODT, Veripred 20, Millipred DP)
	• Prednisone (e.g. Prednisone Intensol, Deltasone, Rayos)
	• Betamethasone (e.g. Celestone Soluspan, Sernivo, Diprolene AF, ReadySharp Betamethasone, Betaloan SUIK, Beta-1)
	• Dexamethasone (e.g. Ozurdex, Maxidex, DexPak 6 Day/10 day/13 Day, LoCort, ZonaCort, ReadySharp dexamethasone, DoubleDex)
	• Hydrocortisone (e.g. Hydrocort, Alphosyl, Aquacort, Cortef, Cortenema, and Solu-Cortef)
	• Methylprednisolone (e.g. Depo-Medrol, Solu-Medrol, Medrol, ReadySharp Methylprednisolone, P-Care D80, and P-Care D40)
	• Deflazacort (e.g. Emflaza)
	• Immunomodulators
	  • Cyclosporine (Sandimmune, Neoral, Gengraf, Restasis MultiDose)
	  • Tacrolimus (Protopic, Envarsus XR, Astagraf XL, Prograf)
	  • Methotrexate (Rheumatrex, Trexall, Otrexup (PF), Xatmep, Rasuvo, Mexate, MTX)
	  • Azathioprine (Immuran, Azasan)
	  • Mercaptopurine (6-MP, Purinethol, Purixan)
	  • Other Immunomodulators not listed above
	• Monoclonal antibody therapy
	  • Infliximab (Remicade)
	  • Etanercept (Enbrel, Benepali, Erelzi)
	  • Adalimumab (Humira)
	  • Secukinumab (Cosentyx)
	  • Tofacitinib (Xeljanz)
	  • Rituximab (Rituxan)
	  • Other monoclonal antibody therapy not listed above
	• Intravenous immunoglobulin treatment (IVIG)

Consequences of Stress Scale (CSS), a scale we developed to measure five functional domains that are frequently dysregulated by stress—namely, cognitive response style, social relationships, eating, sleep, and physical activity. Whereas the PSS-10 criterion ensures that participants have a high enough stress level to benefit from a 12-week precision stress management program, the CSS criterion ensures that participants in the RCT have at least one functional domain that would benefit from a precision intervention.

Although CalSTARS focuses largely on investigating the long-term impacts of early adversity, we intentionally did not establish an inclusion criterion related to ACEs. The reason for this involved our aim to comprehensively assess the full spectrum of ACEs, encompassing both lower and higher levels of adversity. Rather than focusing on ACEs, the longitudinal RCT uses a high PSS-10 score as an inclusion criterion, which is consistent with the trial's goal to reduce perceived stress, a well-known correlate of ACEs.

Sample size and power calculations

The RCT requires 85 participants in each of five functional domains to complete the trial for a total of 425 RCT participants. The 85 participants will be randomized within each domain 1:1:3 [17:17:51] to one of the three study arms: active control (C_A), passive control (C_P), or domain-specific interventions (see Figure 1). Sample size calculations assumed a PSS-10 standard deviation of 7.6, derived from a large 2006 and 2009 U.S. probability sample from a published normative data set (S. Cohen & Janicki-Deverts, 2012). Two power calculations were performed. The first calculation determined that 85 participants for each control arm are needed to detect a difference of ≥3.25 points on the PSS-10 scale with 80% power using a two-sided, two-sample *t*-test. The second calculation compared the combined intervention arms ($n = 255$) with the chosen control arm ($n = 85$). In the primary analysis [analysis of Variance (ANOVA) model], the calculation revealed that a difference of ≥2.65 at Week 16 can be detected with 80% power using a two-sided, two-sample *t*-test.

There are no established minimal clinically important differences (MCIDs) for the PSS-10; however, prior research has shown that the PSS-10 is responsive to psychosocial interventions (Almén et al., 2020; Harris et al., 2006; Willert et al., 2009). Therefore, we chose minimum detectable PSS-10 differences that reflect small-to-moderate standardized effect sizes given the expected standard deviation (i.e. Cohen's *d*) (Cohen, 1988). We anticipate that our repeated-measures design will be more highly-powered than the between-person design used in the power analyses due to minimization of interindividual variability in within-subjects comparisons (Brysbaert, 2019). Moreover, the power analysis does not account for planned adjustments of the intervention effects that may also increase precision of their estimates [i.e. controlling for baseline PSS-10 scores, CSS domain, ACEs, Area Deprivation Index (ADI), age, and sex; see "Data analysis plan"]. Accordingly, we feel that the assumptions underlying the power estimates are reasonable and likely conservative. Ultimately, we plan to recruit enough participants to have 425 with complete

follow-up data in the RCT (allocated 1:1:3 = 20:20:60 in each domain).

Recruitment

Participants will be recruited using email announcements from patient recruitment lists provided by the UCLA Clinical and Translational Science Institute (CTSI). The UCLA CTSI will generate recruitment lists of potential participants who have received care within the UCLA Health system in the past six months, and who meet the study's inclusion and exclusion criteria. To ensure maximum socioeconomic diversity in the sample, participant ADI will be considered during recruitment. ADI quantifies deprivation of the current residential neighborhood on a scale from 1 (*least disadvantaged*) to 10 (*most disadvantaged*), based on census block groups. To account for potential lower response rates from more disadvantaged groups, a greater number of invitations will be sent to individuals in ADI 6–10 (more disadvantaged groups) vs. ADI 1–5 (less disadvantaged groups) using a ratio of 3:2. The expectation is that individuals from more disadvantaged backgrounds will face a greater variety of potential barriers to participating, including work restrictions, childcare duties, and financial considerations, which could reduce their likelihood of responding to invitations, and being able to participate in and complete the study. Response rates and enrollment by ADI deciles will be monitored throughout recruitment, and the ratio may be adjusted accordingly with the goal of ultimately achieving relatively equal representation of individuals from all ten ADI deciles in the final sample.

Consent

Prior to beginning any study procedures, all potential participants will be provided with a detailed explanation of the study's purpose, procedures, and potential risks and benefits. Participation will be entirely voluntary, and participants will have the right to withdraw at any time without penalty. The UCLA study staff is responsible for obtaining informed consent, which will be done remotely by the research staff using the HIPAA-compliant Zoom video platform and an online secure informed consent document. The consent form describes how biological specimens may be analyzed in ancillary studies and explains that all participants may be recontacted for future studies. The consent form also includes an additional consent for genomic data collection and analysis, which is optional.

Allocation and randomization

Participants' scores on the CSS will be used to assign each participant eligible for the RCT to their correct target intervention arm. Participants who are eligible for only one CSS domain (CSS Score > 5) will be assigned to that arm. If a participant has multiple affected CSS domains, their availability for coaching sessions (first order) and self-assessment of the area most impacted by stress (second order) will be taken into account when assigning participants to the intervention arms. To allow for relatively equal group sizes, this procedure will be used with some constraints, whereby some participants who are eligible and available for multiple domains will be randomly assigned to a domain that they do not indicate as their self-assessed area most impacted by stress. Once assigned to a domain, participants will be randomized using a random number generator within each domain to either intervention or control arms on a 3 (intervention):1 (active control):1 (passive control) ratio. Allocation implementation will be performed by a member of the study team.

RCT study design

Explanation for the choice of comparators

The active control group (C_A) will consist of an environmental education program that does not address the topic of stress but matches the intervention group in terms of length of the education sessions, frequency of contact with coach and study personnel, and receipt of actionable, health-relevant information, in order to account for these factors. In contrast, the passive control group (C_P) will not receive weekly content or coaching but will receive the same data collection devices (see below) and complete the same surveys and biospecimen collections. Inclusion of the passive control group will also enable us to conduct a sub-study to evaluate the efficacy of the active control education program on reducing individuals' exposure to health-damaging environmental chemicals, which is interesting and important but not a primary or secondary trial outcome.

Interventions

The PRECISE comprises five arms that address five key domains frequently impacted by stress (see Table 2). The five domains are (a) cognitive response style (Sarin et al., 2005), (b) social relationships (Sandi & Haller, 2015), (c) eating (Yau & Potenza, 2013), (d) sleep (Kalmbach et al., 2018), and (e) physical activity (Stults-Kolehmainen & Sinha, 2014), which will be paired with interventions targeting (a) cognitive restructuring, (b) interpersonal skills, (c) mindful eating, (d) sleep and circadian dysfunction, and (e) mindful movement, respectively.

The five target domains, among others, were selected based on a comprehensive literature synthesis from the Office of Surgeon General Report on Adverse Childhood Experiences, Toxic Stress, and Health (Bhushan et al., 2020). The report defines resilience as "the ability to withstand or recover from stressors, resulting from a combination of intrinsic factors (such as self-regulation or telomere length), extrinsic factors (like safe, stable, and nurturing relationships with family members and others), and predisposing biological susceptibility" (Bhushan et al., 2020). Drawing from this definition, the CalSTARS employs resilience as a framework to assess the effectiveness of aiding individuals in better managing their stress through the provision of education, tools, and resources. Additionally, the Office of Surgeon General Report identifies clinical response strategies to early adversity including patient education to manage stress response such as mindfulness and meditation, supportive social relationships, nutrition, physical activity, and sleep to equip individuals with stress regulation techniques. Therefore, the study yielded the five stress-related domains (i.e. cognitive response style, social

relationships, eating, sleep, and physical activity) as part of the precision stress intervention in response to the previously mentioned overarching framework of resilience.

Although the content of each arm differs, the structure is similar and consists of watching a prerecorded video (~15 min), completing digital modules on the content (20–30 min), attending a live 30 min coaching session on Zoom, and completing a brief 5 min assessment on the material week. Participants will be able to choose from one of two coaching days/times each week. The live coaching sessions will be dedicated to clarifying the content of the weekly digital modules, guiding participants in how to apply the stress-reduction skills to their own lives, and answering questions participants have about the content. Each coaching session will be moderated by a research staff member to limit technical issues and ensure quality control. This research staff member will also document participant attendance at live sessions, along with program module completion, to ensure participant compliance. All coaches are well-established experts in their specific interventions and have five or more years of experience leading group coaching sessions on the topic.

Experimental Arms (E1-E5). Intervention content for the 12-week experimental arms has been developed and/or adapted by experts and focuses on the following:

E1. Cognitive Response Style/Think Well Program participants will learn about identifying and restructuring negative thinking patterns using cognitive restructuring and mindfulness strategies based on the Cognitive Behavior Therapy treatment model (Clark, 2013).

E2. Social Relationship/Be Well Program participants will learn about the importance of social relationships and problem-solving interpersonal conflicts based on the Interpersonal Psychotherapy Therapy treatment model (Rajhans et al., 2020).

E3. Eating/Eat Well Program participants will learn about mindful eating focused on breaking emotional eating cycles, rather than the number of calories or amounts of nutrients consumed, based on the Mindful Eating treatment model (Nelson, 2017).

E4. Sleep/Sleep Well Program participants will learn about the importance of good sleep and maintaining healthy sleep patterns based on the Transdiagnostic Intervention for Sleep and Circadian Dysfunction (TranS-C) treatment model (Harvey et al., 2021; Sarfan et al., 2023).

E5. Physical Activity/Move Well Program participants will learn to move a greater number of their body parts with mindful movement and the importance of adequate physical activity for health based on the self-efficacy arm of the Physical Activity Maintenance Model (Nigg et al., 2008).

Control arms (C_A and C_P)

Active control arm (CA). The Environmental Education/Live Well program will follow the same weekly educational structure as the intervention arms, but stress is not a target topic of the active control videos, coaching sessions, or course materials. Instead, participants will learn about different types of environmental pollution exposures, the health impacts and sources of these exposures, and practical ways to reduce these exposures. In addition, C_A participants will provide lifestyle audits (documenting all diet consumed and household and personal care products used in the 24 hours prior to urine sample collection) as part of the environmental education program. C_A active-control participants will complete the same surveys and use the same data collection devices and kits as the longitudinal experimental-arm participants but, in addition, will wear a personal exposome monitor. Active control participants will be provided at least two (range: 2–4) possible coaching session times per week.

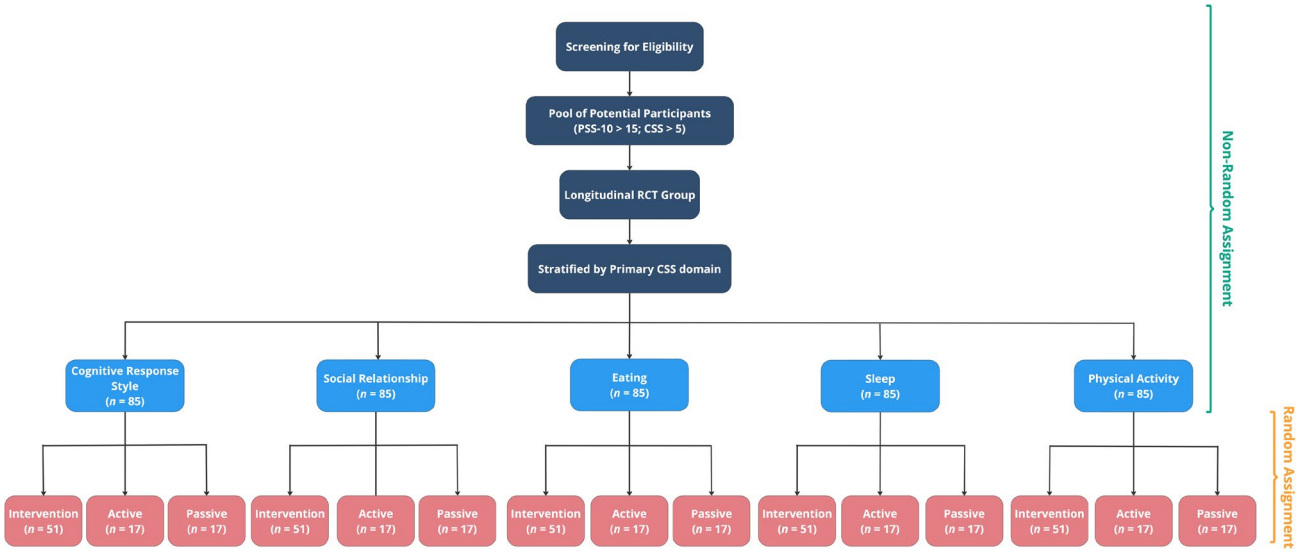

Figure 1. Randomization scheme for the California Stress, Trauma, and Resilience Study (CalSTARS). The two-step randomization framework illustrates that 85 participants in each of the five functional domains ($N = 725$) will be randomized 1:1:3 [17:17:51] to one of the three study arms: active control (C_A), passive control (C_P), or domain-specific stress management intervention.

Passive control arm (CP). As noted above, participants in the passive control (C_P) arm will be assessed longitudinally but not receive any weekly intervention content or coaching. C_P passive-control participants will complete the same surveys and use the same data collection devices and kits as the longitudinal experimental-arm participants but, in addition, will wear a personal exposome monitor similar to C_A participants.

Criteria for discontinuing or modifying allocated interventions, and strategies to improve adherence and retention

There are no special criteria for modifying allocated interventions. Participants are strongly advised to complete a minimum of 9 out of the 12 scheduled digital modules and coaching sessions to maximize the efficacy and benefits derived from the intervention. To improve adherence, we plan to notify participants by email who have stopped syncing their smartwatch data for more than three days. In addition, the smartphone application that participants will use to do the online training modules and surveys will remind them to complete each weekly task multiple times. Participants will also be given an online study calendar document containing specific dates for each task completion and deadlines. To streamline remote instructions, participants will additionally be provided a link to a resource page containing all tutorial videos, written instructions, scheduling page, and a contact form to email questions to the research staff, all in one location. To maximize retention, participant incentives are structured to encourage complete follow-up. For example, participants will receive a small incentive per weekly assessment completed and a bonus if they complete more than 80% of the weekly assessments. Participants are not prohibited from receiving any kind of concomitant care, and post-trial care is not necessary for this type of trial.

Achieving a diverse sample through recruitment and extensive assistance and support

To recruit and retain the most diverse sample possible, we have established a comprehensive set of well-researched protocols to reach under-resourced individuals and lower key barriers to participation. First, the sample will be enriched for relatively disadvantaged individuals by recruiting those in ADI ranks 6–10 (more disadvantaged) vs. ADI ranks 1–5 (less disadvantaged) using a ratio of 3:2. Second, all research staff members will undergo intensive role play training to ensure a respectful and nondiscriminatory environment while interacting with participants and providing accessibility support and assistance. During this training, staff will be taught how to customize and adapt the study protocol to address technical issues, mobility constraints, and logistical challenges, such as difficulty with sample collection and/or drop off. In cases where participants cannot travel to a FedEx shipping center (e.g. due to mobility issues, time constraint, or geographic considerations), the research staff will offer a free FedEx pick-up service for the participant. The support will also include providing devices and technological support to those in need, especially older participants, or those with limited technological experience, to ensure that economic, logistical, and technological issues do not prevent anyone from fully participating in the study.

Third, participants will be able to attend multiple live coaching sessions each week depending on what works best for their schedule. The days and times for these sessions were specifically chosen to include both morning and evening times, as well as days and times that work for individuals from a variety of schedules, occupations, and caregiving responsibilities to maximize inclusivity. Finally, we have created an easy-to-use study webpage that includes multiple ways to contact study personnel (e.g. phone, email), as well as the ability to quickly schedule a troubleshooting appointment during which time participants can speak with a staff member, on the phone or Zoom, to get all of their questions answered. By offering this comprehensive support and assistance, we are deeply devoted to creating an inclusive

Table 2. Checklist of physiological, biological, psychological, and intervention-related activities across baseline only sample and randomized controlled trial.

	Baseline Only Sample	Randomized Controlled Trial						
		Active Control (Live Well Program)	Passive Control (Follow-up Program)	Thinking Style (Think Well Program)	Social Relationships (Be Well Program)	Eating (Eat Well Program)	Sleep (Sleep Well Program)	Physical Activity (Move Well Program)
Physiological								
Smartwatch	✓	✓	✓	✓	✓	✓	✓	✓
Continuous glucose monitor		✓	✓	✓	✓	✓	✓	✓
Exposome monitor[a]	✓	✓	✓					
Biological								
Blood	✓	✓	✓	✓	✓	✓	✓	✓
Saliva (optional)	✓	✓	✓	✓	✓	✓	✓	✓
Stool (optional)	✓	✓	✓	✓	✓	✓	✓	✓
Urine		✓	✓			✓		✓
Psychological								
Self-report surveys	✓	✓	✓	✓	✓	✓	✓	✓
Intervention-related activities								
Weekly assessment		✓	✓	✓	✓	✓	✓	✓
Weekly program modules		✓		✓	✓	✓	✓	✓
Weekly coaching sessions		✓		✓	✓	✓	✓	✓

[a]Exposome monitor is provided to participants in the cross-sectional study as an optional sub-study.

environment that welcomes diverse participants from all backgrounds, resource levels, and age groups.

Blinding

Due to the nature of the intervention, the intervention cannot be completely blinded. Namely, although participants are not told whether they are in an intervention or control arm, participants in both the intervention and active control group will be aware of the educational content they receive, and those in the passive control group will know they are not receiving an intervention program. Blinding participants to the primary subject of the educational content received is not feasible given that the participants need to learn and apply the content to their lives. However, researchers involved in multiomics sample processing and analysis will be blinded to allocation, as will all investigators involved in the data analysis. No procedures for unblinding are necessary given that the study is unblinded.

Outcomes

Cross-sectional analysis. The primary predictors will be ACEs and lifetime stressor exposure, as assessed using the ACEs Questionnaire (Felitti et al., 1998) and Stress and Adversity Inventory (STRAIN) (Cazassa et al. 2020; Slavich & Shields, 2018; Sturmbauer et al., 2019), respectively (see Supplement 2 for details). The primary outcome measures for the cross-sectional analysis will be the multiomics measures including untargeted metabolomics, lipidomics, immune proteins, cytokines, and the microbiome. Due to the limitations of the ACEs scale, we will also evaluate the biological effects of other subtypes of child adversity including childhood resource scarcity, illness, unpredictability, and discrimination (Supplement 2). Exploratory analyses will use physiological and behavioral data derived from the smartwatch and the battery of surveys listed in Supplement 2, which are considered secondary outcomes. We will also evaluate the relation between ACEs, lifetime stressor, and environmental exposures (endocrine disrupting chemicals, air pollution) in the subset of the sample that completed these measures.

RCT analysis. The primary outcome of the RCT is change in perceived stress, assessed using the PSS-10. The PSS-10 is a widely used 10-item questionnaire designed to assess subjective perception of overall stress levels using a 5-point Likert Scale (Cohen et al., 1983; Cohen & Williamson, 1988). The secondary outcomes of the RCT include changes in five domain specific surveys: the Five-Factor Mindfulness Scale short form (cognitive response style domain), Conflict Scale and UCLA Loneliness Scale short form (social relationship domain), Salzburg Stress Eating Scale (eating domain), Insomnia Severity Index (sleep domain), and International Physical Activity Questionnaire short form (physical activity domain). Exploratory outcomes include the multiomics measures (including untargeted metabolomics, lipidomics, immune proteins, cytokines, and the microbiome), physiological measures from the wearable device (including heart rate, heart rate variability, blood pressure, sleep metrics, step count, skin temperature, blood pressure, respiratory rate, and blood oxygen level), and continuous glucose monitoring measures.

The study will also use the battery of validated instruments described in Supplement 2. These surveys broadly assess areas of demographics and environment, cumulative lifetime stressor count and severity, stress response patterns and perceived health, health behaviors, social/interpersonal functioning, emotional regulation and coping, and other relevant psychosocial processes. Process evaluation will occur through the weekly assessments using the PSS-4, CSS, and three questions related to participant engagement and motivation. Further, intervention evaluation questions will be asked of participants during the first follow-up survey to evaluate intervention fidelity and implementation.

Exposome subanalysis. The environmental education program RCT (comparing active and passive controls) will have a primary biological and behavioral outcome. The primary biological outcome will be change in low molecular weight phthalate levels, and the primary behavioral outcome will be change in participants' environmental health literacy. Since environmental health literacy is measured across all arms, other intervention arms can also act as controls for the environmental arm. Secondary outcomes will include changes in other endocrine disrupting chemical (EDC) urinary concentrations including high molecular weight phthalates and environmental phenols, as well as behavioral outcomes such as changes in product use and lifestyle habits that contribute to EDC and air pollution exposures. Exploratory outcomes will include air pollution/particulate matter (PM) exposure and air pollutant compositions.

Participant timeline

Baseline-only sample

The baseline-only sample will participate in a three-week study period consisting of the pre-baseline and baseline phase (see Figure 2; Timeline 1). During the pre-baseline phase, participants will complete the following pre-baseline assessments: (a) online eligibility screener; (b) if eligible, an intake session to review consent form; and (c) Baseline Survey 1. Participants will be required to complete the Baseline Survey 1 before a research package containing the data collection study materials is sent out. This decision to place the Baseline Survey 1 in the pre-baseline phase will help ensure that the research package containing costly data collection devices such as the smartwatch, monitors, and sample collection kits are sent to those willing to complete necessary tasks and provide study data.

Once the pre-baseline phase is over and participants receive the research package containing all of the data collection devices, the baseline phase will begin and include the following assessments in chronological order: (a) Device Guide Zoom call to provide instruction on how to setup the smartwatch and if applicable, an exposome monitor; (b) Sample Kit Zoom call to provide instructional guidance to

collect biospecimens (e.g. blood, stool, saliva); and (c) collection and shipment in which participants collect specimens at a scheduled date and time, complete the Baseline Survey 2, and return the research package. Following this three-week study period, the baseline only participants will be finished with the study.

RCT sample

Participants in the RCT will complete a 27-week protocol consisting of a pre-baseline, baseline, study, and follow-up phase (see Figure 2; Timeline 2). The pre-baseline and baseline phase of the study is identical to the baseline-only sample except RCT participants will receive additional continuous glucose monitor devices and urine kits (C_A, C_P, E3 and E5 only).

During the 12-week study phase, the precision stress management intervention RCT is performed as described above. Participants in the intervention and active control arms will complete the following study phase activities: (a) wear the smartwatch and regularly sync it to a HIPAA-compliant smartphone app called My Personal Health Dashboard (MyPHD; (Bahmani et al., 2021), (b) complete weekly program modules on the MyPHD smartphone app, (c) attend weekly Zoom group coaching sessions with a health coach, and (d) complete brief weekly assessment surveys. All intervention content will be delivered using the HIPAA-compliant MyPHD app and REDCap platform. Participants in the passive control arm (C_P) will only (a) wear the smartwatch and sync it to MyPHD and (b) complete the brief weekly assessment surveys.

During the post-intervention follow-up phase of the study, participants will be asked to: (a) continue to wear the smartwatch for another 12 weeks, (b) rewear a Continuous Glucose Monitor (CGM) and exposome monitor (C_P, C_A only), (c) recollect biospecimen(s) [e.g. blood, urine (C_A, C_P, E3 and E5 only)], and (d) complete Follow-up Survey 1. Once these assessments are completed, participants will go about their normal lives wearing the smartwatch until the last week of the study period (Week 27), at which point they will collect their final biospecimen(s) [e.g. blood, urine (C_A, C_P, E3 and E5 only] and complete Follow-up Survey 2. This will conclude the study period for the RCT participants.

Data collection and management

Surveys

Participants will complete all self-report questionnaires using REDCap, a secure web-based platform that provides: (a) an intuitive interface for validated data capture, (b) audit trails for tracking data manipulation and export procedures, (c) automated export procedures for seamless data downloads to common statistical packages, and (d) procedures for data integration and interoperability with external sources (Harris et al., 2009, 2019).

Physiological and other devices

Smartwatch and app. The smartwatch participants will receive was developed by SensOmics and is designed to collect physiological and behavioral data for research cohort use. It has six biosensors (photoplethysmography (PPG), electrocardiography (ECG), galvanic skin response (GSR), skin temperatures, and a 6-axis accelerometer and gyroscope) that can measure heart rate, heart rate variability (HRV), blood pressure, respiratory rate, blood oxygen level (SpO2), skin temperature, steps, and sleep time. The smartwatch also provides sensor raw data (PPG at 10 Hz, G-sensor at 10 Hz, ECG at 125 Hz). Participants will be required to wear the smartwatch for a minimum of 18 hours for five days during the week. The smartwatch must also sync daily to the MyPHD app. The MyPHD app directly collects health data from the SensOmics smartwatch and securely transfers the de-identified and encrypted data for further analysis. Through MyPHD, participants will be able to have their wearable device data automatically uploaded to be accessible by the study team.

Continuous glucose monitor (CGM). All RCT participants will be sent a Dexcom G6 Pro CGM to wear at two time points: first, during the baseline study phase (for ten days), and second, after the 12-week intervention (for ten days). Components of Dexcom G6 Pro include: auto-applicator (one touch-applicator allows for simple sensor insertion), sensor (monitors interstitial glucose levels through a small wire inserted just underneath the skin, sending a signal to the transmitter), and transmitter (single-use, disposable transmitter is fastened on top of the sensor and auto-starts for expedited startup time). The CGM will be in blinded mode so participants will not be able to see their glucose values during the study; however, the information will be shared with them at the end of the study. Participants will wear the CGM on either their abdomen or upper arm. A research staff member will teach each participant how to place and use the CGM.

Personal exposome monitor. The personal exposome monitor is smaller than a pack of cards (100 g) and measures particulate matter exposure (PM2.5, PM1, PM4, PM10) with GPS; it also has filters for assessing cumulative chemical and biological exposures. Participants will be asked to carry the device with them at all times. If the person is sedentary at home or work, these devices can be placed nearby (i.e. in the same room). Study participants will be instructed to recharge the unit each night to enable continuous monitoring over a 10-day period.

Biological sample collection

To minimize variability in samples from differential shipping times, all participants will be instructed to collect biological samples during business hours on Monday-Thursday and drop them off at a local FedEx station the same day before 4 pm for overnight delivery to the sample processing lab. In case a participant is unable to collect their sample(s) Monday-Thursday, weekend collection on Saturday or Sunday will be allowed. Blood and urine samples will be stored in the refrigerator, and stool and saliva will be stored at room temperature over the weekend. Weekend collections must be dropped off at FedEx on Monday before 4 pm for overnight shipping. All samples will be stored at −80 C for later analysis.

Blood. All participants will self-administer micro blood draws that collect capillary blood from the upper arm using TASSO M20 devices, which are rated as less painful than finger stick devices (Knitza et al., 2022). All participants will draw blood first thing in the morning when they wake up before eating, drinking (except water), or exercise. The TASSO-M20 collects four dried whole capillary blood samples of 17.5 µL each. The total volume is less than 2% of what a standard 5 mL blood draw with a tube would collect. The expected risks of this blood collection are minimal.

Saliva. All participants who consent to having their genetic information analyzed and used for research will provide a saliva sample collected using the Oragene Discover (OGR-600) Self-Collection Kit for DNA sampling (DNA Genotek Inc.). This kit enables participants to easily collect saliva samples in the comfort of their home. OGR-600 collects a high quantity of saliva (2 mL), which will be used for whole exome and/or genome sequencing. The median DNA yield is 110 µL. This kit is painless and has a reliable self-collection process.

Stool. All participants who consent to stool collection will collect a small sample of their stool using the OMNIgene•GUT (OMR-200.100) Microbiome Collection Kit (DNA Genotek Inc.). This kit enables participants to easily collect fecal samples in the comfort of their home. Collection kit configuration (OMR-200.100) includes: spatula (OMR-200), 2 toilet accessories packaged in a plastic envelope (OM-AC1), Bio-specimen bag (MO-3), and 2-way mailers shipping box with peelable adhesive strip for sample return. Once participants void stool into the toilet basin, they will use the spatula provided to scrap a small portion of the stool into the collection tube and then seal it tightly for shipping.

Urine. Selected arms of the RCT–namely, the active (C_A) and passive control (C_P) arms, eating (E3) arm, and physical activity (E5) arm–will receive a mail-in urine kit consisting of a urine collection cup, instructions, and return shipping package. The specific gravity of the urine samples will also be assessed upon arrival to the lab to enable adjustment for effects of various levels of hydration prior to freezing or processing.

Exposome filters. The personal exposome monitors contain a biological and chemical filter, which will collect participants' cumulative exposures for each 10-day period the exposome monitor is worn.

Electronic health records

Electronic health record (EHR) data will be available and analyzed for participants who have had health care visits in the UCLA Health system. The amount and type of information available for each participant will vary based on a number of factors, including how long the individual has been a patient, the number and type of health care visits attended, and the type and extent of health care services delivered. Expected data will provide information regarding participants' health care, diagnoses, treatment(s), lab results, and more. EHR data will be used both to identify potential supplementary outcomes in the cross-sectional arm (e.g. associations between ACEs and disease diagnoses or clinical laboratory results), and to help increase precision in estimating the effects of ACEs, adult stress, and the intervention on multiomics endpoints in both arms. Specifically, variables obtained from EHRs may be used as covariates or moderators to help isolate effects that are specific to ACEs and perceived stress, after accounting for variance attributable to disease processes. For example, research has found that cardiovascular disease is characterized by changes to a number of metabolic processes (Ussher et al., 2016). Therefore, it is possible that the effects of the intervention on metabolomic outcomes differ between those with and without diagnosed cardiovascular conditions. How EHR data are incorporated into follow-up analyses will depend both on the information provided from these records and the frequency of common health problems in the sample (i.e. whether we have adequate power to test their effects or

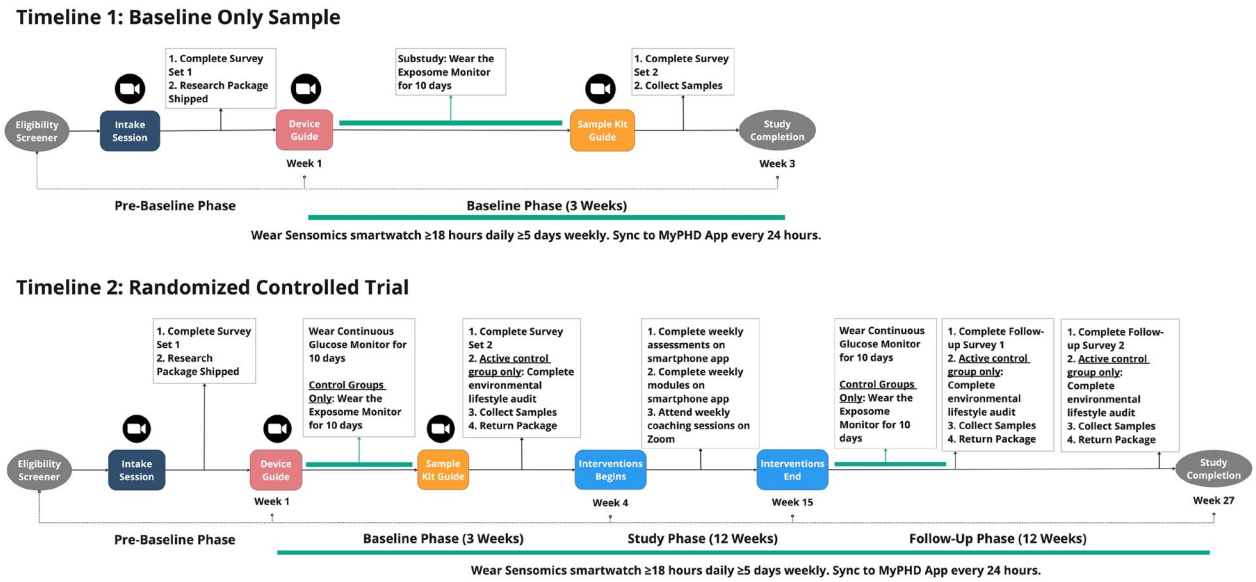

Figure 2. Overview and timeline of the California Stress, Trauma, and Resilience Study (CalSTARS). Shown is the timeline and description of the data collection procedures for the Baseline Only Sample (Timeline 1, top) and Randomized Controlled Trial (Timeline 2, bottom).

should instead perform sensitivity analyses excluding individuals with diagnosed conditions).

Sample analysis

Multiomics assays. Genomic sequencing (whole exome sequencing) will be performed on saliva samples. Planned multiomics assays on blood microsamples include metabolomics/lipidomics, targeted immune protein panel, and proteomics (Shen et al., 2023). Lipidomics assays will be performed using the Lipidizer Platform using our previously described method (Contrepois et al., 2018). Untargeted metabolomics will be assayed using hydrophilic interaction liquid chromatography (HILIC) and reverse phase liquid chromatography (RPLC). Immune proteins including cytokines, chemokines, and growth factors will be assessed. A subset of samples will be analyzed for untargeted proteomics using Proximity Extension Assay (PEA) technology, which combines an antibody-based immunoassay with polymerase chain reaction (PCR) and readout using next-generation sequencing to determine the relative concentrations of hundreds of proteins simultaneously (Olink, 2020). Planned gut microbiome profiling on stool samples (baseline time point only) includes 16S rRNA analyses.

Urinary endocrine disrupting chemical (EDC) assay. Urine samples will be assessed for thirteen endocrine disrupting chemicals: bisphenols (A, S, F), parabens (methyl-, ethyl-, butyl- and propylparaben), phthalates (monoethyl, mono-n-butyl, mono-2-ethylhexyl, mono-2-ethylhexyl, mono-2-ethylhexyl, mono-2-(-ethyl-5-hydroxyhexyl), and mono-(2-ethyl-5-carboxy pentyl)), and other chemicals (benzophenone-1, benzophenone-3, triclosan) using high-pressure liquid chromatography (HPLC).

Exposome monitor filter analysis. DNA and RNA will be extracted from the biological filters and sequenced, and liquid chromatography coupled with high-resolution mass spectrometry will be used to analyze chemical filters.

Data management

All study participants will be given a unique identification code, which will be used to link their data from various sources.

Confidentiality. All data will be kept strictly confidential and stored in HIPAA-compliant locations. Remote surveys and interventions will be delivered using REDCap, a secure, online, HIPAA-compliant survey platform, with the ability to link individual survey responses to unique identifying codes that can be preset using unique links. To gather data collected from the devices, participants will be asked to download and use the MyPHD app. MyPHD has already undergone Data Risk Assessment (DRA #665) for use in a similar approved studies that involve Stanford University (Stanford IRB #55577 and #57022). In addition, because we will be mailing participants several research items including the smartwatch, TASSO blood collection devices, microbiome kit, and CGMs, we will also ensure that no identifying information is included on any shipping labels for packages containing participant specimens and/or devices. De-identified specimens will then be shipped to the Snyder Lab at Stanford for processing.

Data analysis plan

Cross-sectional analyses

We will use descriptive statistics to characterize the demographic characteristics of the sample and summarize participants' stressor exposures and functioning, based on the ACEs questionnaire, STRAIN, PSS-10, and five domain-specific CSS scores across all 725 participants. We will also summarize these measures across ADI deciles and repeat this analysis in the baseline-only subsample. We will then examine associations between multiomics biological measures of immune and metabolic health, physiological measures (e.g. heart rate variability), and self-reported psychological and health metrics (as measured by surveys). The primary analysis will examine associations between ACE exposure and multiomics biological measures using a multi-faceted analysis approach. Where necessary, we will correct for multiple testing using the positive false discovery rate. In addition, pathway analysis will be performed with associated analytes with a q-value <0.2.

Additional planned analyses will examine how the different ACE categories (e.g. abuse, neglect), other childhood adversity exposures, and sub-types of lifetime stressor exposure relate to multiomics, physiological, and self-reported psychological and physical health outcomes. We will also use STRAIN scale responses to examine associations between stressor severity, frequency, and exposure timing on stress-related biology. Additional survey and demographic factors will be used to explore potential moderators of relations between ACEs, lifetime stressor exposure, and biological function (e.g. sex differences). Secondary outcomes may also be obtained from EHRs (e.g. clinical laboratory data, disease diagnoses), depending on the quantity and quality of information gleaned from these records. Finally, we plan to conduct exploratory multivariate and network analyses of the multiomics data to assess covariation between different biological systems both within and outside the context of stress, which may provide information more broadly about whether stress is associated with overall systems-level dysfunction. This is not an exhaustive list of the exploratory analyses planned for the cross-sectional arm; detailed strategies will be developed and registered prior to data analysis.

RCT analyses

Analyses will be performed for the intention-to-treat population and reported to comply with the Consolidated Standards of Reporting Trials (CONSORT) statement (Boutron et al., 2017; Moher et al., 2010). We will use descriptive statistics to characterize demographic and ADI features, and summarize (a) baseline measures of stress, including the ACEs questionnaire and PSS-10, as well as (b) baseline measures of current health that may reflect a participant's stress level, including inflammatory markers and physiological data (e.g. heart rate variability) by intervention group (i.e. intervention vs. control), intervention arm domains, control group type, and total

across all groups. The Consequences of Stress Scale (CSS) will also be analyzed to determine if the scale enables the normalization of specific biobehavioral pathways based on individuals' primary needs.

The primary outcome analysis will use a generalized estimating equation (GEE) analysis of covariance (ANCOVA) model to estimate the mean (95% confidence interval) differences in PSS-10 scores at Week 16 between the experimental arm (E) and, first, the passive control arm (C_P) and, second, the active control arm (C_A). The model will be adjusted for baseline PSS-10 levels and CSS domain, as well as baseline risk factors for perceived stress including ACEs, ADI, age, and sex, and will account for repeated measures within participants using robust standard errors. If the mean of PSS-10 scores is significantly lower in the E vs. C arms (i.e. the global null hypothesis that these means are equal is rejected), we will then repeat the above analysis stratified by CSS domain to estimate differences in the efficacy of the five interventions. To account for multiple comparisons, we will apply Tukey's/Dunnett's strategy. A preliminary analysis comparing C_A to C_P will be conducted to evaluate the efficacy of C_A in reducing stress. If C_A is shown to reduce stress compared to C_P, then the experimental arms will show lower efficacy in comparison with C_A than C_P. This analysis will aid in interpreting the results of the primary analysis.

Secondary analyses will use similar ANCOVA models as well as other models depending on data type and the specific research question at hand. Any subgroup analyses—such as high vs. low ACE exposure, etc.—will first test for a Subgroup x Trial Group (i.e. intervention vs. control) interaction; if this interaction is significant ($p < 0.05$), then results will be estimated separately by subgroup. In addition to assessing the moderating effect of ACEs on intervention efficacy, exploratory analyses will also examine the impact of the intervention on ACEs-related biology, per se. That is, information about relations between ACEs and multiomic profiles obtained from analyses of baseline and cross-sectional data will be used to test whether all or certain experimental arms lead to changes in biological pathways related to ACE exposure (relative to control arms). These secondary analyses will lay the groundwork for future precision interventions designed to mitigate the lasting sequelae of ACEs. For example, we plan to create a post-hoc model in which we will use the biological data collected to develop a multimodal predictive algorithm to identify who benefits most from the precision stress management intervention, and, if possible, why. Using this retrospective model, we will then develop a personalized medicine algorithm that can leverage an individual's multi-omic and psychological data to produce personalized stress treatment regimens that reduce stress and improve health markers to maximize overall treatment efficacy, specifically.

A detailed statistical analysis plan will be developed prior to commencing analyses and we have no interim analyses planned. Issues with missing data and potential participation bias will be handled following the strategies outlined in the *Methods to handle protocol non-adherence and missing data* section below.

Exposome analysis. The primary exposome analysis will compare the active control arm (C_A)—an environmental education program—with the passive control no-intervention arm (C_P) to evaluate the efficacy of C_A in reducing EDC concentrations, specifically phthalate levels. Similar to the preliminary comparison of C_A versus C_P, analyses will be conducted using link functions and distributional assumptions tailored to the outcome variables.

Methods to handle protocol non-adherence and missing data. After all data is collected, we will explore the extent of missing data and the potential causes of missingness. If data are found to be missing at random (MAR) (i.e. data are missing as a function of other observed variables), we will conduct analyses on all available data using mixed-effects models that are robust to MAR data (Mallinckrodt et al., 2003; Schielzeth et al., 2020). In the event that missingness reduces the final sample size below the target determined by the power analysis, we will perform multiple imputation using multivariate imputation by chained equations (Zhang, 2016). Results will be provided both for analyses involving fully observed and imputed data. If there is evidence that data are not missing at random (NMAR) (e.g. if missing data is more likely for those with high stress levels), then we will develop a model to predict probability of missingness and will conduct sensitivity analyses using pattern mixture modeling (Gray et al., 2020; Ratitch et al., 2013; Staudt et al., 2022).

Two additional follow-up sensitivity analyses will (a) include only data from participants without missing data (i.e. complete case analysis) and (b) adjust for potential participation bias. Regarding the latter, eligible participants whose schedules do not align with the coaching sessions will be excluded from the longitudinal arm of the study. Drop-outs, exclusions, and non-response can all contribute to the final sample differing systematically from the full pool of eligible participants. Without correction, participation bias can distort associations between exposures and outcomes in volunteer-based studies (Schoeler et al., 2023; Tripepi et al., 2010). To adjust for participation bias, we will use inverse probability weighting to produce survey weights that minimize differences between the final sample and eligible pool on key variables (Chesnaye et al., 2022; Mansournia & Altman, 2016). We will conduct sensitivity analyses by testing the primary models again while including these weights.

Oversight and monitoring

CalSTARS does not have a formal oversight committee or external data monitoring committee due to the noninvasive, low-risk nature of the intervention. The research team comprises investigators from UCLA, Stanford University, and UCSF, and meets weekly to discuss any issues that arise during the conduct of the trial and includes the study biostatistician. If needed, issues requiring input from the entire investigative team are communicated to the team for input. The study team also meets monthly with leadership from the study's funder, the California Initiative to Advance Precision Medicine (CIAPM), to provide regular updates and address any challenges that arise.

Safety evaluation

Certain self-report questionnaires may yield information that would require action to ensure safety. Namely, the STRAIN asks participants whether there was ever a period of time when they or someone they know have experienced emotional and physical abuse. These questions focus primarily on early life, but participants could also identify a recent abuse experience. In this case, participants may report current abuse of themselves or of vulnerable personnel (e.g. child, dependent adult, or elder). To address these questions, in the consent form, we have described the limits of confidentiality and, in particular, that the research team may not be able to keep confidential any disclosure or endorsement of thoughts of or actual harm to the self or others. In the event that a participant reveals information about known or reasonably suspected incidents of abuse or neglect of a child, dependent adult or elder including, but not limited to, physical, sexual, emotional, and financial abuse or neglect, California law requires action to be taken to mitigate the risk, and participants in this study are notified of that requirement.

In instances of risk for possible abuse or suicide, the lead Principal Investigator (PI), Dr. George Slavich, will be the mandated reporter, and will contact the participant and authorities as appropriate. Any investigator who is not a mandated reporter will not report information about known sexual or physical abuse of a child, dependent adult or elder which may be disclosed during the research, but will immediately inform Dr. George Slavich, who will make the report. In the event that a participant reveals that they are thinking about possibly killing themselves or if they answer yes to a question about having thoughts about suicide or being better off dead, the research staff will ask them more questions about the thoughts to clarify whether there is an intention or plan to harm. Depending on the nature of the situation and degree of risk, the research staff will (in order of severity): (a) provide self-help information; (b) provide information for a crisis line; (c) provide a referral for treatment; (d) work with them to contact their personal physician, trusted family member, or therapist to discuss their thoughts of harming themselves; or (e) work with them to immediately get to a hospital or police station for safety and/or call for emergency help, as indicated. The study coordinator will immediately contact Dr. George Slavich, who will make direct contact with the participant and determine the correct course of action given the risk level present.

Adverse event reporting and harms

Clinical adverse events (AEs) will be monitored throughout the study by the research staff interacting with participants. Since the study procedures are not greater than minimal risk, serious AEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including serious AEs) they will be reported to the Institutional Review Board (IRB) in accordance with Office of Human Protections (OHRP) IRB Reporting Procedures for Unanticipated Problems, Noncompliance, Suspension, or Termination. AEs that do not meet prompt reporting requirements will be summarized in narrative or other format and submitted to the IRB at the time of continuing review (if continuing reviews are required) or will be tracked and documented internally by the study team but not submitted to the IRB (if continuing reviews are not required).

Plans for communicating important protocol amendments to relevant parties

Changes to the study protocol will be presented to the IRB for review, and communicated to the investigative team and funder.

Discussion

In conclusion, although numerous studies have examined the deleterious effects of ACEs on health, we are not aware of any studies that have used a multiomics, systems biology perspective to examine these associations. Indeed, most studies on this topic so far have focused on only a few analytes, thus greatly limiting our understanding of how ACEs are related to biological dysregulation at the systems level. To advance this work, we designed CalSTARS, which has five main points of novelty:

1. By collecting a large and highly diverse sample of participants, we will examine associations between ACEs and stress-related psychology and biology in a highly diverse sample of participants.
2. Using highly powerful multiomics approaches, we will explore stress biology from a systems perspective.
3. We will use a stressor characteristic perspective to determine if all ACEs are associated with dysregulated stress and disease biology in an equivalent manner or, alternatively, if there are stressor-specific effects that differ by ACE type.
4. Beyond testing for possible unique effects of specific ACEs, we will use enriched survey measurements to determine which assessments of early life stressor exposure [e.g. ACEs questionnaire (Felitti et al., 1998), STRAIN (Slavich & Shields, 2018), early-life resource scarcity (Hill et al., 2016), early-life unpredictability (Mittal et al., 2015)], are associated with the greatest biopsychosocial dysregulation in adulthood.
5. Finally, we will use comprehensive surveys that can measure experiences with exclusion and inclusion across multiple marginalized groups. Specifically, we will measure both identity-specific (i.e. discrimination) and identity-agnostic life stressors (i.e. general stressful life events).

In addition to the cross-sectional study, we know of no precision stress management intervention programs that tailor treatment selection based on careful patient profiling. We aim to address this important issue with the second goal of our study, which is to demonstrate how tools from precision medicine can be used to enhance stress management and improve patient outcomes. The longitudinal RCT that we designed for this purpose has six main points of novelty:

1. By identifying and targeting participants' greatest needs in five stress-related domains (i.e. cognitive response style, social relationship, eating, sleep, and physical activity), we will establish a novel framework for delivering targeted interventions in this critically important space (see Gilgoff et al., 2024).
2. By giving participants the ability to self-identify the functional domain in which they feel they need the most help, we will enhance participant engagement and compliance, and provide a model for treating participants as active partners in the scientific process.
3. We will test the feasibility and scalability of our novel precision stress management intervention program with the ultimate goal of translating it directly into community settings, thus achieving the goal of using translational science principles to readily assimilate the program into clinical and community settings.
4. The study possesses a unique design as an entirely remote, large-scale study that assesses various aspects of health including physiology, biology, and self-reports, providing a model for future de-centralized research that is more accessible to participants in diverse situations.
5. The RCT is complemented by a well-powered, cross-sectional study that will inform analyses testing the effects of the intervention on ACE-associated biology pathways.
6. The study also recognizes that stressor exposures do not occur in isolation and examines how such exposures interact with a wide variety of other environmental exposures and factors that are also known to have negative biopsychosocial effects.

Looking forward, we aim to use the data derived from this study to help develop a more comprehensive understanding of how ACEs interact with a variety of risk and resilience factors to shape broadband psychological and biological functioning in adulthood. Second, we hope that the insights we glean can be used to inform future precision stress management programs that target stress-related biological dysfunction based on each individual's specific stress biotype. Finally, by testing the PRECISE, we hope to reduce perceived stress and increase psychosocial resilience by investigating the extent to which this scalable, precision stress management program disrupts stress-related processes that promote chronic disease risk and early mortality. By pursuing these aims, we hope to foster healthier, more resilient individuals and communities worldwide.

Ethics and dissemination

This study protocol was approved using UCLA as the single Institutional Review Board, IRB Protocol #22-000637, with Stanford University as a relying site. Participants will have the right to withdraw from the study for any reason, and at any time, without it affecting their routine care or relationship to UCLA or Stanford. Consent for publication is unnecessary, as no individually identifiable data or images will ever be presented or published. See Supplement 3 and Supplement 4 for the informed consent forms.

Dissemination plans

We plan to disseminate the results of this study in scientific journals and at professional conferences. In addition, we will disseminate the main results to members of the California Stress, Trauma, and Resilience (CAL STAR) Network by developing a presentation and information dissemination policy and strategy to help ensure that the information reaches all relevant populations, stakeholders, and interest groups.

Plans to give access to the full protocol, participant level-data and statistical code

Fully de-identified, participant level-data and statistical code will be made available as part of the process of publishing the results in journals.

Trial status

The study is ongoing as of September 2024. The first wave of RCT participants was recruited between July 5th and July 31st, 2023, and the second wave of RCT participants was recruited between January 22nd and February 22nd, 2024, with an anticipated RCT end date of September 30th, 2024. Recruitment of the cross-sectional, baseline-only sample commenced in the fall of 2023 and will be completed by September 30th, 2024.

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Disclosure statement

AJB is cofounder and consultant to Personalis and NuMedii; consultant to Mango Tree Corporation, Samsung, 10x Genomics, Helix, Pathway Genomics, and Verinata (Illumina); served on paid advisory panels or boards for Geisinger Health, Regenstrief Institute, Gerson Lehrman Group, AlphaSights, Covance, Novartis, Genentech, Merck, and Roche; is

a shareholder in Personalis and NuMedii; a minor shareholder in Apple, Meta (Facebook), Alphabet (Google), Microsoft, Amazon, Snap, 10x Genomics, Illumina, Regeneron, Sanofi, Pfizer, Royalty Pharma, Moderna, Sutro, Doximity, BioNtech, Invitae, Pacific Biosciences, Editas Medicine, Nuna Health, Assay Depot, Vet24seven, and several other non–health-related companies and mutual funds; has received honoraria and travel reimbursement for invited talks from Johnson & Johnson, Roche, Genentech, Pfizer, Merck, Lilly, Takeda, Varian, Mars, Siemens, Optum, Abbott, Celgene, AstraZeneca, AbbVie, Westat, and many academic institutions, medical or disease-specific foundations and associations, and health systems; received royalty payments through Stanford University for several patents and other disclosures licensed to NuMedii and Personalis; and received research funding from NIH, Peraton, Genentech, Johnson & Johnson, US Food and Drug Administration, Robert Wood Johnson Foundation, Leon Lowenstein Foundation, Intervalien Foundation, Priscilla Chan and Mark Zuckerberg, the Barbara and Gerson Bakar Foundation, March of Dimes, Juvenile Diabetes Research Foundation, California Governor's Office of Planning and Research, California Institute for Regenerative Medicine, L'Oréal, and Progenity, all outside the submitted work. MPS is a cofounder and scientific advisor of Personalis, SensOmics, Exposomics, Qbio, January AI, Fodsel, Filtricine, Protos, RTHM, Iollo, Marble Therapeutics, Crosshair Therapeutics, and Mirvie. He is a scientific advisor for Jupiter, Neuvivo, Swaza, and Mitrix. Due to the conflict of interest with Sensomics, MPS will only have access to de-identified, repository level data. The other authors declare no conflicts of interest with respect to this work.

Data availability

There are no data associated with this article.

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